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TOXICOLOGICAL ASSESSMENT OF ABATE (TRADE NAME) (O,O,O',O'-TETRA--ETC(U)
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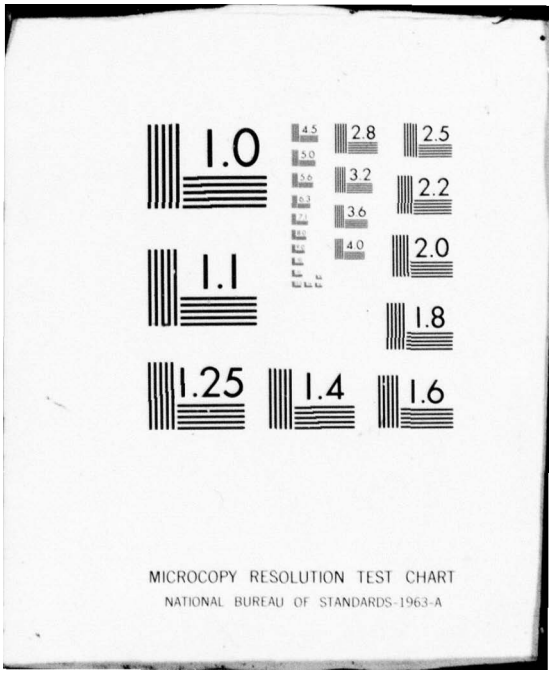
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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

(14) USAEHA-

PHASE I

STUDY NO. 75-51-1302-80

(6) TOXICOLOGICAL ASSESSMENT OF ABATE® (Trade Name)
(0,0,0',0'-TETRAMETHYL-O,O'-THIO-DI-P-PHENYLENE PHOSPHOROTHIOATE)
DERMAL PENETRATION OF RADIO-LABELED ABATE
SEPTEMBER 1977 - OCTOBER 1979 - Phase I,

(10) Hubert L. Snodgrass, Jr

(11) 23 Apr 80

(12) 17

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

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4. TITLE (and Subtitle): Phase I, Toxicological Assessment of ABATE(0,0,0',0'-Tetramethyl-0,0'-Thio-Di-Phenylene Phosphorothioate) Dermal Penetration of Radio-Labeled ABATE, Study No. 75-51-1302-80, September 1977 - October 1979	5. TYPE OF REPORT & PERIOD COVERED
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18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

ABATE	pediculicide
absorption	percutaneous
dermal penetration	radio-labeled
distribution	0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-Phenylene
intravenous	Phosphorothioate

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The dermal penetration of radio-labeled ^{14}C-ABATE was measured in rats, rabbits and dogs. Absorption was assessed by monitoring excreted radioactivity in urine and feces for 7 days and analysis of representative tissue specimens at the end of the test period. It is concluded that topically applied ABATE should not present a dermatotoxic hazard to man following a single application and absorption would be expected to be less than 3 percent of the applied dose. No evidence of bodily retention or pooling of the radioactive moiety has been demonstrated in these tests.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

Mr. Snodgrass/pam/AUTOVON
584-3980

HSE-LT

23 APR 1980

SUBJECT: Phase I, Toxicological Assessment of ABATE (0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-Phenylene Phosphorothioate), Dermal Penetration of Radio-Labeled ABATE, Study No. 75-51-1302-80, September 1977 - October 1979

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section
Walter Reed Army Medical Center
Washington, DC 20012

A summary of the pertinent findings of the inclosed report follows:

a. The dermal penetration of radio-labeled ^{14}C-ABATE was measured in rats, rabbits, and dogs. Absorption was assessed by monitoring excreted radioactivity in urine and feces for 7 days and analysis of representative tissue specimens at the end of the test period.

b. It is concluded that topically applied ABATE should not present a dermatotoxic hazard to man following a single application and absorption would be expected to be less than 3 percent of the applied dose. No evidence of bodily retention or pooling of the radioactive moiety has been demonstrated in these tests.

FOR THE COMMANDER:

JOHN F. MAZUR
MAJ, MSC
Director, Laboratory Services

1 Incl
as

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Cen on Tox, NRC
Supt, AHS (HSA-IPM)

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT/WP

PHASE I
STUDY NO. 75-51-1302-80
TOXICOLOGICAL ASSESSMENT OF ABATE®
(0,0,0',0'-TETRAMETHYL-0,0'-THIO-DI-P-PHENYLENE PHOSPHOROTHIOATE)
DERMAL PENETRATION OF RADIO-LABELED ABATE

1. AUTHORITY. Letter, HSPA-H, US Army Health Services Command, 20 October 1976, subject: Investigational New Drug Application for ABATE Pediculicide with incl, Ltr, AFPCB, Armed Forces Pest Control Board, 13 September 1976, same subject.

2. SUMMARY AND CONCLUSION.

a. The percutaneous penetration of ^{14}C-labeled ABATE® was measured in three animal species. Absorption was assessed by monitoring excreted radioactivity in urine and feces daily for 7 days and analysis of representative tissue specimens at the end of the test period. Urinary excretion was the major elimination pathway of absorbed chemical in each species, measuring 24.6 and 6.7 percent of the applied dose for rabbits and rats respectively. Dogs showed only minimal ABATE urinary excretion of 0.5 percent of the applied dose through 7 days. Nearly all of the unabsorbed compound was recovered in dogs from a nonocclusive patch which protected the area and apparently trapped the evaporating compound. Protective patches were not monitored in rats and rabbits but would be expected to contain a similar ratio of activity as demonstrated in the dog. Tissue specimens from various body depots monitored in each species showed only trace amounts or the absence of radioactivity 7 days after application, indicating little affinity of the chemical for tissue binding.

b. It is concluded that the topically applied pediculicide ABATE should not present a dermatotoxic hazard to man following a single application and absorption would be expected to be less than 3 percent of the applied dose. Primary metabolic elimination of the chemical should occur within the first 24 hours via urinary excretion and be essentially complete after 3 days. No evidence of bodily retention or pooling of the radioactive moiety has been demonstrated in these tests. These conclusions, however, are self-limiting and are based on experimentally controlled situations. Variations, such as dermatologic absorption thresholds of the chemical, may or may not manifest themselves and have yet to be documented.

®ABATE is a registered tradename for American Cyanamid Co, Princeton, NJ 08540.

3. BACKGROUND.

a. The Armed Forces Pest Management Board (AFPMB) is coordinating the registration of the pediculicide ABATE with the Food and Drug Administration (FDA). Registration is required since a formulation of this compound has been produced for standardization in the control of lice in military programs. Negotiations with FDA for a field test program have indicated the need for the development of an Investigational New Drug Application (IND).

b. To assist in the development of this IND, the US Army Environmental Hygiene Agency (USAEHA) was requested to conduct studies on the dermal absorption and distribution of ^{14}C ABATE in animals.

4. PURPOSE.

a. This study was designed to determine the penetration of the proposed topically applied pediculicide, ^{14}C-labeled ABATE, through the intact skin of rabbits, rats and dogs. Absorption and distribution of the ABATE was determined by monitoring radioactivity in excreted urine and feces for 7 days following topical application and in tissues at necropsy.

b. The study involves the topical application of ^{14}C-labeled ABATE to the clipped mid-lumbar area of an animal's back. Application is made to an area of the back which has been demarcated with petrolatum to contain the compound. The site is then covered with a nonocclusive patch to eliminate contamination of excreta through normal evulsion of skin. Aliquots of urine and feces are collected daily for 7 days, oxidized to CO_2, and activity counted on a liquid scintillation counter. At the end of the collection period, the animals are sacrificed and sections of organs and tissues are analyzed for retained radioactivity. A second group of animals is given the labeled compound intravenously to assure that systemic elimination occurs in that specific animal species. For each mode of administration, all animals are randomly placed in individual metabolism cages, retained thusly throughout the study and receive food and water ad libitum.

5. MATERIALS. Radiolabeled ABATE-(ring ^{14}C) was purchased from New England Nuclear (NEN), Boston, MA. The compound was received as a solution in benzene, packaged in a sealed ampoule reportedly containing 5.0 millicuries (mCi) of radioactivity and a mass of 166.5 milligrams (mg). It was designated as Lot No. 922-237, Assay No. 113871, 113974 and was noted to have a specific activity of 14.0 millicuries/millimole (mCi/mmol). The

radiochemical purity was reported as greater than 98 percent based on comparative peak area measurements. The NEN assay utilized a hexane:ether (7:3 V/V) solvent system and thin layer chromatography (TLC) silica gel C. The solvent used in the animal studies was methyl alcohol, obtained from Fisher Scientific Company, Fair Lawn, NJ, as certified ACS Methanol. The preparation of solutions for use in these studies involved crushing the ampoule in 20 ml methanol leaving a primary stock solution of 8.33 mg ABATE/ml with an activity of 250 microcuries (μCi)/ml. Further dilutions were made also in methanol to obtain aliquots for intravenous (iv) and dermal (pc) administration.

6. ANIMALS.

a. Absorption and distribution studies of ^{14}C ABATE were conducted by USAEHA using male New Zealand White rabbits, male Sprague-Dawley rats and male beagle dogs. Rabbits were purchased from Marland Breeding Farms, Hewitt, NJ, and the dogs from Hazleton Laboratories, Vienna, VA. The rats were selected from USAEHA breeding colonies.

b. All animals were maintained on commercial chow* and water ad libitum with a 12-hour light-dark sequence. Ambient conditions were 24°C $\pm$2°C and 45-55 percent relative humidity. All animals were housed individually in stainless steel metabolism cages throughout the test.

7. METHODS.

a. One week prior to application of the test compound, beginning on a Monday, all animals were placed in metabolism cages and allowed to acclimate and establish a regular urine output. Blood samples from test dogs were also drawn during the control period. An aliquot of 5 ml control urine sample (2.0 ml heparinized blood) was retained for background ^{14}C levels following oxidation of the urine and blood to CO_2.

b. Aliquots of urine (0.2 ml), blood (0.2 ml), and tissues (0.25 to 0.5 g) were oxidized using a Harvey Biological Materials Oxidizer (Model LF 521), the evolved CO_2 absorbed in 15 ml of Oxifluor®-CO_2, and radioactivity measured using a Beckman Liquid Scintillation Counter (Model LS200). Appropriate background and standards were run concurrently. Feces were collected, weighed and homogenized in toto in water. Radioactivity was measured in a 0.2 ml aliquot as for urine.

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* Lab Canine Diet 5006, Purina® Rabbit Chow® Checkers® G and rat Formulab Chow® 5008 are registered trade names of Ralston Purina Co., St Louis, MO. ®Oxifluor-CO_2 is a registered trade name of NEN, Boston, MA.

c. The compounds were first given intravenously to the three species in order to determine the efficiency of the renal excretion process. Intravenous administration consisted of injecting methanol solutions of ABATE into the marginal ear vein of the rabbit, the cephalic vein of the dog or the femoral vein of the rat. Blood was drawn from dogs prior to injection, immediately after, and at timed intervals thereafter to document disappearance rates from the circulation. Urine from rabbits, dogs and rats was collected daily for 7 days, the volumes measured and normalized to a specific gravity of 1.024 g/ml. The details of the solutions, volumes and activity injected are shown in the following table.

TABLE. DETAIL OF ABATE SOLUTION ADMINISTRATION

Animal Species	Method of Administration	Administration: Total Volume	Total Activity	Total Mass ABATE	Skin Area Covered and Rate	Concentration of Solution
Rat	iv	0.05 ml	1.0 µCi	33 µg	--	20 µCi/ml (660 µg/ml)
	pc	0.1 ml	1.0 µCi	33 µg	8.25 cm^2 @ 4 µg/cm^2	10 µCi/ml (330 µg/ml)
Rabbit	iv	0.1 ml	1.0 µCi	33 µg	--	10 µCi/ml (330 µg/ml)
	pc	0.1 ml	1.0 µCi	33 µg	8.25 cm^2 @ 4 µg/cm^2	10 µCi/ml (330 µg/ml)
Dog	iv	0.1 ml	1.0 µCi	33 µg	--	10 µCi/ml (330 µg/ml)
	pc	0.1 ml	1.0 µCi	33 µg	8.25 cm^2 @ 4 µg/cm^2	10 µCi/ml (330 µg/ml)
Dog	iv	1.0 ml	10.0 µCi	330 µg	--	10 µCi/ml (330 µg/ml)
	pc	0.2 ml	10.0 µCi	330 µg	8.25 cm^2 @ 40 µg/cm^2	50 µCi/ml (1650 µg/ml)

d. Topical application to all species was made to the clipped mid-lumbar region by means of an autopipette. The area of application was always 8.25 cm^2 with the quantity of application varying from 4 µg/cm^2 in all species to 40 µg/cm^2 in a dog study. The area was demarcated with petrolatum to contain the repellent while the solvent evaporated. Following topical application, the area was covered by a nonocclusive patch to prevent contamination of excreta by the normal exfoliation of skin. Details of the administrations are shown in the Table.

e. The urinary and fecal excretion of ^{14}C was quantitated over a 7-day study period. Excretion rates for each day's collection were calculated as percent of the initial injected or applied dose. In addition, immediately following the final urine collection, all animals were sacrificed in an effort to determine the point of deposition of retained labeled compound. Vital organs were excised and wet-weighed intact. Representative specimens were taken from brain, lungs, liver, kidneys, spleen, testes, normal skin, muscle, fat (omental), bone (femur), and skin from the application site. One-fourth to one-half gram sections of each specimen were oxidized to CO_2 and radioactivity counted. Calculations are based on counts/wet gram of tissue.

Calculations for the ^{14}C studies were as follows:

$$\mu Ci/ml = \frac{\text{sample count (DPM) - background (DPM)}}{\text{(Efficiency) } (2.22 \times 10^6) \text{ (aliquot volume)}}$$

$$\text{Efficiency} = \frac{\text{actual DPM count - background from oxidation}}{\text{known DPM added}}$$

$$1\ \mu Ci = 2.22 \times 10^6\ DPM$$

aliquot volume = fraction of sample oxidized

MDQ = minimum detectable quantity

$$= (3)\sqrt{\frac{\text{DPM background}}{\text{counting time (min)}}}$$

This value is added to the background count for the day. Any count equal to or below this value is considered to be $\leq$MDQ. Nominal values run about 3 DPM for a 20-min counting period.

$\mu Ci/g$ tissue = Same calculation as for $\mu Ci/ml$. Aliquot volume would be weight of sample oxidized.

f. Approval for the use of ^{14}C-labeled compounds was obtained from the Chairman, Ionizing Radiation Control Committee, USAEHA. All manipulations of test compounds, including the disposal of waste materials are handled in accordance with USAEHA Reg 40-14.

8. RESULTS.

a. The amounts of ^{14}C activity found in urine, feces, organs and tissues at 7 days in rabbits, rats and dogs following intravenous administration of radiolabeled ABATE are shown in Appendices A thru C. The activity found in similar determinations following dermal application, plus skin application sites and, in the dog, recovery from the protective patches, are shown in Appendices D thru F. These data are presented as a percentage of the applied ^{14}C dose found in the urine, feces and organs while the activity in the various tissues is shown as μCi/gram of tissue.

b. Urinary excretion of topically applied ^{14}C material was greatest in the rabbit, less in the rat and least in the dog (<1 percent). Fecal elimination following dermal dosing accounted for a large percentage of the overall activity recovered in the dog and rat but contributed substantially less in the rabbit. Negligible amounts of activity, except for the 1-5 percent of the applied dose found at the skin application site, was found at 7 days in the organs and tissues of any animal following dermal administration. The protective patch in the 10 µCi dog study was found to contain almost 90 percent of the total activity applied. The patches were not analyzed for radioactivity in the other dog, rat and rabbit studies.

c. Blood levels of radioactivity following intravenous administration of 10 µCi in the dog are shown in Appendix G. The results are expressed as counts per minute (CPM) and are from samples taken over a 24-hour period. An equation for the disappearance of radioactivity from the dog's blood following intravenous administration can be expressed by the exponential equation as follows:

$$\log_{10} CPM = 0.336e^{-0.567t} + 2.05\ e^{-0.004t}$$

where t = time in hours.

d. Urinary recovery of radioactivity following intravenous dosing was greatest in the rabbit (approximately 45 percent recovery) with a lesser amount in the rat and dog (approximately 10-18 percent recovery). Fecal elimination accounted for over half the activity recovered in the dog but only about 28 percent in the rabbit and 14 percent in the rat.

9. DISCUSSION.

a. These studies assume that distribution and excretion of the test compound are essentially the same following both intravenous and dermal administrations. The results obtained do not deny this supposition. However, the low overall recovery following intravenous dosing indicates the material is actively metabolized, not pooled in any tissue or organ, and is eliminated in a manner not monitored in this study. The most logical elimination route would be exhaled material and studies are being considered to examine this portal.

b. The wide variations between species in excretion of this compound is not unexpected since a seven-fold variance between rabbit and man has been reported by Bartek, LaBudde and Maibach (1972).[1] Other studies have indicated that penetration potential of the dog lies between the monkey and pig (McCreesh, 1965).[2] If man's porosity is close to these latter species as suggested by Bartek, et al,[1] and Wester and Maibach (1975),[3] it is expected that the human penetration figure should lie in the area of about 3 percent of an applied dosage of ABATE.

HUBERT L. SNODGRASS, JR.
Biological Laboratory Technician
Toxicology Division

APPROVED:

ARTHUR H. McCREESH, Ph.D.
Chief, Toxicology Division

APPENDIX A

TOTAL PERCENTAGE OF RECOVERED ^{14}C-LABELED ABATE IN URINE AND FECES FOLLOWING INTRAVENOUS ADMINISTRATION

		Urine	Feces	Total
Rat, Male	$\bar{x}$	17.67	6.88	24.56
1 µCi	s.d.	4.98	1.72	
Rabbit, Male	$\bar{x}$	46.89	7.79	54.67
1 µCi	s.d.	3.78	1.67	
Dog, Male	$\bar{x}$	11.79	23.05	34.84
1 µCi	s.d.	1.92	10.52	
Dog, Male	$\bar{x}$	9.57	10.47	20.04
10 µCi	s.d.	1.05	11.65	

APPENDIX B

PERCENTAGE OF URINARY EXCRETION OF ^{14}C-LABELED ABATE FOLLOWING INTRAVENOUS ADMINISTRATION

		Day 1	2	3	4	5	6	7	Total
Rat, Male	$\bar{x}$	12.24	2.96	1.17	0.54	0.35	0.22	0.20	17.67
1 μCi (33 μg)	s.d.	2.22	1.88	0.78	0.24	0.15	0.07	0.03	4.98
Rabbit, Male	$\bar{x}$	37.09	4.43	1.68	2.27	1.02	0.58	0.57	46.89
1 μCi (33 μg)	s.d.	3.04	1.36	0.40	1.27	0.16	0.17	0.22	3.78
Dog, Male	$\bar{x}$	9.33	1.45	0.46	0.34	0.25	<MDQ	<MDQ	11.79
1 μCi (33 μg)	s.d.	1.58	0.74	0.22	0.30	0.43			1.92
Dog, Male	$\bar{x}$	5.29	2.96	0.37	0.37	0.30	0.19	0.09	9.57
10 μCi	s.d.	2.07	2.73	0.36	0.17	0.09	0.09	0.02	1.05
(330 μg)									

Study No. 75-51-1302-80, Sep 77 - Oct 79

APPENDIX C

MEAN VALUES FOR DEPOSITION OF
^{14}C-LABELED ABATE IN ORGANS AND TISSUES
7 DAYS FOLLOWING INTRAVENOUS ADMINISTRATION

	Organs (% Applied Dose)						Tissues (µCi/gram Tissue)			(normal)
	Liver	Lung	Spleen	Kidney	Testes	Brain	Muscle	Fat	Bone	Skin
Rat, 1 µCi	0.045	0.213	0.003	0.002	<MDQ	<MDQ	<MDQ	3.7×10^{-4}	5×10^{-6}	1.2×10^{-5}
Rabbit, 1 µCi	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ
Dog, 1 µCi	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ
Dog, 10 µCi	0.233	0.01	<MDQ	0.01	0.01	<MDQ	1×10^{-6}	8×10^{-4}	1×10^{-4}	3.1×10^{-4}

MDQ - Minimum detectable quantity.

APPENDIX D

TOTAL PERCENTAGE OF RECOVERED ^{14}C-LABELED ABATE
FOLLOWING DERMAL ADMINISTRATION

		Urine	Feces	Skin Application Area	Protective Patch A	Protective Patch B	Total
Rat, Male	$\bar{x}$	6.72	10.95	1.91			19.58
1 µCi	s.d.	3.80	14.54	0.72			
Rabbit, Male	$\bar{x}$	24.57	9.05	5.40			39.02
1 µCi	s.d.	15.12	9.02	2.61			
Dog, Male	$\bar{x}$	Not	Not	2.06			--
1 µCi	s.d.	calculated	calculated	2.15			
Dog, Male	$\bar{x}$	0.51	0.87	1.44	76.21	11.98	91.01
10 µCi	s.d.	0.52	0.71	0.91	16.73	8.84	

A - Removed at 24 hours
B - Removed at 7 days.

APPENDIX E

URINARY EXCRETION OF ^{14}C-LABELED ABATE
FOLLOWING DERMAL ADMINISTRATION
(Percent Applied Dose)

		Day 1	2	3	4	5	6	7	Total
Rat, Male	$\bar{x}$	1.47	1.98	1.07	0.97	0.68	0.32	0.23	6.72
1 µCi	s.d.	0.65	0.86	0.76	0.84	0.45	0.17	0.07	3.80
(33 µg ABATE)									
Rabbit, Male	$\bar{x}$	8.21	6.55	3.22	2.78	1.66	1.22	0.94	24.57
1 µCi	s.d.	3.42	2.63	1.48	1.35	0.84	0.93	1.05	15.12
(33 µg ABATE)									
Dog, Male	$\bar{x}$	<MDQ	<MDQ	0.21	<MDQ	<MDQ	<MDQ	<MDQ	Not
1 µCi	s.d.			0.19					calculated
(33 µg ABATE)									
Dog, Male	$\bar{x}$	0.15	0.18	0.12	0.03	0.01	0.01	0.00	0.51
10 µCi	s.d.	0.12	0.27	0.22	0.05	0.02	0.02	--	0.52
(330 µg ABATE)									

Study No. 75-51-1302-80, Sep 77 - Oct 79

APPENDIX F

MEAN VALUES FOR DEPOSITION OF
^{14}C-LABELED ABATE IN ORGANS AND TISSUES
7 DAYS FOLLOWING DERMAL ADMINISTRATION

	Organs (% Applied Dose)						Tissues (μCi/gram Tissue)			(Normal)
	Liver	Lung	Spleen	Kidney	Testes	Brain	Muscle	Fat	Bone	Skin
Rat, 1 μCi	0.03	<MDQ	<MDQ	0.001	<MDQ	0.001	<MDQ	4.6×10^{-5}	<MDQ	<MDQ
Rabbit, 1 μCi	<MDQ	0.02	0.001	0.003	<MDQ	0.0003	2.0×10^{-5}	4.9×10^{-5}	1.4×10^{-5}	3×10^{-6}
Dog, 1 μCi	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ
Dog, 10 μCi	0.03	0.02	<MDQ	<MDQ	<MDQ	<MDQ	<MDQ	2×10^{-5}	3×10^{-6}	<MDQ

MDQ - Minimum detectable quantity.

Study No. 75-51-1302-80 , Sep 77 - Oct 7º

APPENDIX G

BLOOD LEVELS OF ^{14}C RADIOACTIVITY IN THE DOG
FOLLOWING INTRAVENOUS ADMINISTRATION OF 10 µCi ABATE

	(minutes)								
TIME:	5	10	15	30	60	120	240	480	24 hr
Mean (± s.d.) Activity CPM	239 (28)	218 (24)	214 26	214 (42)	177 (32)	138 (24)	110 (19)	102 (9)	73 (8)

APPENDIX H

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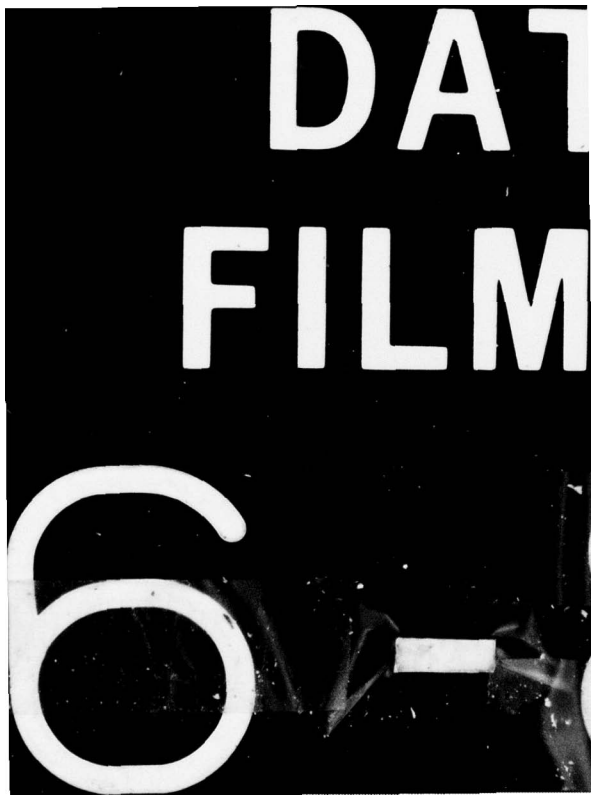
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